Visualizing Alzheimer's disease pathology

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2016

document version
Publisher's PDF, also known as Version of record

SUMMARY

This thesis focused on the implementation of amyloid PET in clinical practice. The main aims of this thesis were:
1) to compare clinical interpretation of amyloid PET with CSF biomarkers;
2) to investigate the clinical utility of amyloid PET;
3) to examine the association of amyloid PET with Alzheimer risk factors.
In this chapter, the main findings of this thesis are summarized and placed within the broader context of current AD research, which is followed by methodological considerations and concluded by future perspectives.

Molecular imaging of Alzheimer pathology
The first part of this thesis provides a general introduction in molecular imaging of Alzheimer pathology. **In Chapter 1.2** we provided an overview of current literature on amyloid and tau tracers for *in vivo* detection of amyloid and tau pathology. In non-demented subjects, amyloid PET has a high predictive accuracy for future conversion to AD dementia. In dementia patients, amyloid PET positivity can also be found in other syndromes besides AD, such as posterior cortical atrophy, logopenic aphasia and Lewy bodies dementia. Furthermore, tau PET tracers are currently under development. Histopathology and first-in-human tau PET studies indicate a more tightly association with neurodegeneration and cognitive decline compared to amyloid PET.

Detecting Alzheimer pathology: Amyloid PET and CSF biomarkers
The second part of the thesis compared clinical interpretation of amyloid PET with CSF biomarkers as markers for Alzheimer pathology. In **Chapter 2.1** we investigated the concordance between amyloid pathology on [^{11}C]PIB PET and CSF biomarkers for Alzheimer pathology, including soluble forms of the proteins amyloid β(1-42) ($A\beta_{42}$), and tau. In a memory clinic sample of cognitively normal subjects, MCI patients and demented patients, concordance between [^{11}C]PIB PET and CSF $A\beta_{42}$ was 84%. Most often, discordance was seen in MCI and AD patients with (borderline) normal CSF $A\beta_{42}$ levels and positive [^{11}C]PIB PET. When a more lenient $A\beta_{42}$ cut-off point or a combination of $A\beta_{42}$ and tau was used, concordance with [^{11}C]PIB PET was even higher. Overall, these findings provide convergent validity for the use of both types of biomarkers as measures of AD pathology in a memory clinic population. In **Chapter 2.2** CSF $A\beta_{42}$ cut-off points were defined based on [^{11}C]PIB PET and compared with cut-off points currently used in clinical practice. Analyses were performed in a cohort including 433 subjects from 5 different European centers. Amyloid PET-based CSF $A\beta_{42}$ cut-off points were higher and reduced inter-center variability when compared with current clinical cut-off points. Exploratory analyses showed that subjects with a positive [^{11}C]PIB PET and a (borderline) normal CSF $A\beta_{42}$ level had higher CSF tau and p-tau levels and were more often MCI or AD dementia patients. These findings suggest that CSF $A\beta_{42}$ cut-off points based on amyloid PET may be helpful to determine more generally applicable cut-off points for CSF biomarkers. Furthermore, subjects with (borderline) normal CSF $A\beta_{42}$ and a positive [^{11}C]PIB PET scan may be more likely to have AD-related amyloid pathology according to their increased tau levels in CSF and clinical diagnosis.

Clinical use of amyloid PET
In the third part of this thesis we investigated the clinical use of amyloid PET. In **Chapter 3.1** several parametric imaging methods were compared to determine the optimal approach for visual assessment of [^{11}C]PIB PET images in a memory clinic sample. Both 60 and 90 minutes BP_{ND} images showed excellent inter-reader agreement, whilst agreement was good to moderate for SUVr and SUV images. Inter-method agreement varied substantially between readers, although BP_{ND} images consistently showed the best performance. Therefore, our findings indicate that the RPM2 method, providing [^{11}C]PIB BP_{ND} images, is the method of choice for optimal visual interpretation of [^{11}C]PIB PET scans. In **Chapter 3.2** the diagnostic utility of [^{18}F]flutemetamol PET in early-onset dementia patients was assessed. A total of 211 tertiary memory clinic patients suspected of having mild early-onset dementia,

in whom diagnosis remained unclear after routine diagnostic work-up, underwent [^{18}F]flutemetamol PET imaging. PET scans were positive in 77% of patients with a pre-PET AD diagnosis and in 33% of patients with a non-AD diagnosis. After disclosure of PET, 19% of diagnoses were changed and in 37% PET results led to a change in patient management. These findings show that [^{18}F]flutemetamol PET has added value over a standardized work-up in early-onset dementia patients with an uncertain clinical diagnosis.

Alzheimer pathology and AD risk factors

In the fourth part of this thesis we examined the association of amyloid pathology with Alzheimer risk factors in preclinical and clinical AD. In **Chapter 4.1** the associations of AD risk factors with amyloid pathology in cognitively normal elderly were analyzed. Besides the well-known risk factors for AD, which are older age and *APOE* ε4 genotype, presence of subjective memory complaints (SMC) was also associated with pathological amyloid deposition. More specifically, the association of SMC with amyloid pathology was restricted to *APOE* ε4 carriers and younger participants. These findings indicate that, besides older age and *APOE* ε4 genotype, SMC may also be indicative for amyloid pathology and may help enrich a cognitively normal elderly cohort for amyloid pathology in secondary prevention trials. In **Chapter 4.2** the relationships between age and both *in vivo* fibrillary amyloid deposition and glucose metabolism in AD patients were assessed. Although the extent of amyloid deposition or glucose hypometabolism did not differ between younger and older AD patients, regional differences were found with younger patients showing increased [^{11}C]PIB binding and decreased [^{18}F]FDG uptake in the parietal cortex. Furthermore, in younger patients both increased amyloid pathology and lower metabolic activity in the parietal cortex were related with poorer visuo-spatial functioning. These findings provide evidence that neuropathology may contribute to distinct clinical presentations seen in younger and older AD patients.